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Appeal 2016-002684 Application 12/663,197 Technology Center 1600

Before JOHN G. NEW, TIMOTHY G. MAJORS, and DAVID COTTA, *Administrative Patent Judges*.

NEW, Administrative Patent Judge.

DECISION ON REQUEST FOR REHEARING

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¹ Appellant states that the real party-in-interest is Haplomic Technologies Pty, Ltd. App. Br. 2.

Appellant has filed a Request for Rehearing (hereinafter the "Request") under 37 C.F.R. § 41.52(a)(1) for reconsideration of our Decision of December 15, 2017 (hereinafter the "Decision").

The Decision reversed the Examiner's rejections of claims 16, 20, 22, 24, and 25 as unpatentable under 35 U.S.C. § 102(b) over X. Liu et al., *Preparation of Single Rice Chromosome for Construction of a DNA Library Using a Laser Microbeam Trap*, 109 J. BIOTECH. 217–26 (2004). Decision 19. However, the Decision affirmed the Examiner's rejection of claims 16, 20, 22, and 24–27 as unpatentable under 35 U.S.C. § 101 as being directed to nonstatutory subject matter. *Id*.

In the Request, Appellant seeks reconsideration of our Decision affirming the Examiner's rejection of claims 16, 20, 22, and 24–27 under 35 U.S.C. § 101. Specifically, Appellant argues: (1) the Board incorrectly determined that claim 16 is directed to one of the judicially-created exceptions to 35 U.S.C. § 101; (2) the Board failed to address that the combination of steps recited in the claims is one that was novel and nonroutine in the art of DNA methylation analysis at the priority date of the present application; (3) the Board did not address that the problem that is solved by the combination of steps is one rooted in the art of DNA methylation analysis; and (4) the Board erred in finding that: "[t]he mental step of making a determination of whether two methylated sites are cis or trans therefore constitutes an abstract idea, another judicially-created exception to Section 101." Request 3, 7 (quoting Decision 18). Finally, Appellant "wish[es] to address the Board's 'preemption' argument." *Id.* at 8. We address each of these arguments in turn.

A. Whether claim 16 is directed to a judicially-created exception to 35 U.S.C. § 101

Appellant argues that the Board concluded that the claim is directed to a "phenomenon of nature," but failed to indicate what that natural phenomenon is. Request 3. Appellant points to page 12 of the Decision, which, Appellant contends, explains that the claims recite a method of isolating and describing the location of methylated sites on DNA isolated from individual chromosomes and determining whether any two of the methylated sites are present in *cis* or *trans* configurations. *Id.* According to Appellant, the Decision further explains that the method describes locations of methylation sites already present in the DNA and does not require alteration of the methylation sites of the isolated DNA.² *Id.* Appellant speculates that the Board implied that the claims are somehow directed to the natural phenomenon of an isolated DNA molecule, but contends that this

² Appellant also notes in fn.1 (mislabeled fn. 11) that claim 26 recites a step of reacting the isolated DNA with bisulfite to convert unmethylated cytosines to uracil, thus transforming the isolated molecule into another kind of molecule. Request 3. In the Final Office Action, the Examiner found that treating the genomic DNA with bisulfite represented routine conventional activity and that the steps do not significantly transform the naturally existing methylated bases since bisulfite does not have any effect on the naturally existing methylated bases. Final Act. 2–3. Appellant, in the Appeal Brief, argued that "Appellant submits that these more particularized methods of analysis [i.e., bisulfite treatment] yet further remove the subject matter claimed in claims 26 and 27 from the realm of mere "abstract ideas." App. Br. 15. However, in the briefs below, Appellant did not make the argument that bisulfite treatment (which Appellant's Specification admits is well known in the art) transforms the molecule by replacing methylated cytosines with uracil. Because Appellant did not raise this issue in the Appeal, the argument is not considered in the Request. See 37 C.F.R. § 41.51(a)(1).

interpretation is not correct; rather, Appellant argues, the claims are directed to a process for determining the structure of a DNA molecule, not to an isolated DNA molecule. *Id*.

We are not persuaded that the Board misapprehended or overlooked Appellant's arguments. Reviewing the claims, the Examiner concluded that: "[T]he claims are directed to determining the presence or absence of one or more methylated bases on the DNA and determining whether any two methylated bases are present in cis on the DNA molecule, and, as such, are directed towards a phenomenon of nature." Decision 10 (citing Ans. 9). The Board adopted the Examiner's conclusion, stating:

Appellant's claim [16] recites a method of isolating and describing the location of methylated sites on DNA isolated from an individual chromosome or chromatid and determining whether any two of the methylated sites are present in *cis*, i.e., both located on the maternal or paternal chromosome from which it was isolated. *See* Spec. 5. As such, Appellant's claims are directed to a method of describing the location of methylated sites that are already present in the chromosomal DNA within the cell. Appellant's claims do not, explicitly or inherently, require any alteration of the methylation sites in the isolated DNA, merely a description of whether two methylated sites are *cis* (i.e., located on the same chromosome) or *trans* (located on sister chromosomes). *See* Spec. 5. Nor are Appellant's claims of detecting methylation sites linked to any particular location on a particular chromosome, chromatid, or fragment thereof.

Decision 12. Both the Examiner and the Board thus agreed that Appellant's claim 16 is directed to determining whether the sites of methylation on a portion of isolated DNA are *cis* or *trans*. Appellant's claim 16 is not directed to altering, or in any other way changing, the *cis* or *trans* configuration of the isolated DNA, but is directed rather to detecting the configuration of methylated sites that are already present in the DNA

molecule *in situ* prior to its isolation from the cell. In much the same way, the general determination of the nucleotide sequence of a naturally-occurring DNA *in situ* is a phenomenon of nature. *See*, *e.g.*, *Ariosa Diagnostics*, *Inc. v. Sequenom*, *Inc.*, 788 F.3d 1371, 1376 (Fed. Cir. 2015). As such, we conclude again that, because the DNA is methylated in its *cis* or *trans* configuration prior to isolation, and because Appellant's claims are directed merely to determining the configuration that exists prior to such isolation, Appellant's claims are directed to a naturally-occurring phenomenon, i.e., a "phenomenon of nature," and, therefore, to a judicially-created exception to Section 101.

B. & C. The Board allegedly failed to address that the combination of steps recited in the claims is novel and non-routine in the art of DNA methylation analysis and that the problem that is solved by the combination of steps is one rooted in the art of DNA methylation analysis

Appellant next argues that the Board failed to address Appellant's assertion that the combination of isolation of an individual chromosome, or a part thereof, together with analysis of the methylation pattern of the isolated chromosome or part thereof, was not "well-understood, routine, conventional activity" in the field of methylation analysis of genomic DNA at the time the present application was filed. Request 4. According to Appellant, the Board reads the claims as a step directed to a natural phenomenon in isolation from additional steps that recite "well-understood, routine, conventional activity." *Id.* (quoting Decision 16). Appellant contends that, under the jurisprudence of the Supreme Court and the Federal Circuit, as well as the Patent Office's examination guidance and training

materials, a claim at issue must be reviewed for a combination of elements that describes an "inventive concept." *Id.* at 5.

By way of example, Appellant points to Example 29 of the Life Science Examples provided in the USPTO's training materials published in May 2016³ (hereinafter the "Guidance") which, Appellant argues, presents facts similar to those of the present appeal. Request 5. Particularly, Appellant asserts, the fact pattern of (hypothetical) Example 29 postulates (and similar to the state of the art with respect to isolation of individual chromosomes), that porcine antibodies had been used in the prior art, but not for purposes of diagnosing a hypothetical disease. *Id.* According to Appellant, the Example's hypothetical claim 3⁴ is patentable because:

[S]ignificantly, there is no evidence that porcine antibodies were routinely or conventionally used to detect human proteins such as JUL-1. Thus, the claim's recitation of detecting JUL-1 using a porcine antibody is an unconventional step that is more than a mere instruction to "apply" the correlation and critical thinking

Guidance 10.

³ USPTO, Subject Matter Eligibility Examples: Life Sciences, 1–31 (May 2016).

⁴ Hypothetical claim 3 of the Guidance' Example 29 recites:

^{3.} A method of diagnosing julitis in a patient, said method comprising:

a. obtaining a plasma sample from a human patient;

b. detecting whether JUL-1 is present in the plasma sample by contacting the plasma sample with a porcine anti-JUL-1 antibody and detecting binding between JUL-1 and the porcine antibody; and

c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected.

step (the exception) using well-understood, routine or conventional techniques in the field.

Request 5 (quoting Guidance 13).

Similarly, Appellant asserts, in appealed claim 16, the step of analyzing the isolated chromosome to determine the presence or absence of one or more methylated bases in the DNA molecule and determining whether any two methylated bases are present in *cis* or in *trans* on the DNA molecule was not routinely applied to isolated chromosomes at the time the present application was filed. Request 6. Alternatively, argues Appellant, it was not routine in the art of DNA methylation analysis to use individual chromosomes (or chromatids or fragments thereof) as the starting material for methylation analysis of genomic DNA or, at least, there is no evidence in the record that would support a conclusion that either combination was routine in the art. *Id*.

Appellant repeats the argument presented previously, that the claimed use of an isolated individual chromosome as the starting material for the methylation analysis solves a problem systematically embedded in the nature of methylation analysis at the time the present application was filed. Request 6. Appellant contends that our reviewing court has held that claims to inventions that solve a problem central to the art in which they are practiced can be patent-eligible despite being directed to a judicial exception. *Id.* (citing, e.g., *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1256 (Fed. Cir. 2014)). In so finding, Appellant asserts, the court indicated that:

These claims stand apart [from claims found ineligible for patenting] because they do not merely recite the performance of some business practice known from the pre-Internet world along

with the requirement to perform it on the Internet. Instead, the claimed solution is necessarily rooted in computer technology in order to overcome a problem specifically arising in the realm of computer networks.

Id. (quoting *DDR*, 773 F.3d at 1257). Appellant argues that the court also relied upon a finding that the claims as a whole described an invention that was not using the internet in a merely routine or conventional manner; similarly, Appellant asserts, and as in the Guidance's Example 29, the court relied in part on the non-routine nature of the combination of claim elements. *Id.*

According to Appellant, the Decision does not give any substantial rebuttal at all to Appellant's argument that the claims solve a problem rooted in the art of genomic DNA methylation analysis and that the claims recite a technological step that was not routinely applied in the art of genomic DNA methylation analysis that solves that problem. Request 6. Appellant asserts that both of these aspects of the present claims have been found in Federal Circuit decisions to support patent eligibility of claims. *Id.* Therefore, Appellant argues, the Board's alleged failure to consider the combination of elements in the claims on appeal with whatever abstract ideas or natural phenomena are recited in the claims, and the combination of the recited steps that provide a method that is a practical application of those abstract ideas or natural phenomena that is not conventional or routine in the art at the time *Id.* at 6–7.

Appellant's argument does not persuade us the Board overlooked or misapprehended relevant points of fact or law in the Decision. As we have explained, we find that independent claim 16 is directed to a phenomenon of nature, *viz.*, the state of *cis* or *trans* methylation of a DNA molecule as it

occurs *in situ*. Having so determined, the second step of our two-step analysis under *Mayo Collaborative Services v. Prometheus Laboratories*, *Inc.*, 566 U.S. 66 (2012), requires that we next consider the elements of the claims on appeal both individually and "as an ordered combination" to determine whether additional elements "transform the nature of the claim" into a patent-eligible application such that the claim limitations amount to "significantly more" than a patent upon the ineligible concept itself. 566 U.S. at 78, 79.

Claim 16 requires three steps: (1) substantially isolating a DNA molecule; (2) analyzing the DNA to determine whether any of the DNA molecule sequence's sites are methylated; and (3) determining whether the methylated sites are present in *cis* on the isolated DNA molecule. The claim thus expressly embraces *any* method of analyzing the isolated DNA molecule for methylation sites.

Claim 25, which depends from claim 16, names some of these methods, including: "DNA sequencing using bisulfite treatment, restriction landmark genomic scanning, methylation-sensitive arbitrarily primed PCR, Southern analysis using a methylation-sensitive restriction enzyme, methylation-specific PCR, restriction enzyme digestion of PCR products amplified from bisulfite-converted DNA, and combinations thereof." However, Appellant does not argue that any of these methods were not previously well known in the art as methods of localizing methylated DNA sites. *See* Spec. 4 ("In another form of the invention where the step of

analyzing is performed on DNA, the modification is methylation.⁵ The analysis may be implemented using any suitable methodology, however typically the step of analyzing the one or more sites for the presence or absence of methylation comprises a method selected from the ... [methods recited in claim 25]"). In short, Appellant's claims are directed to determining, by any means, including means well known in the art, the naturally-occurring *cis* or *trans* position of methylated sites on a sequence of isolated DNA.

We therefore do not find persuasive Appellant's arguments that the limitations of the claims add "significantly more" to the natural phenomenon of *in situ* methylated DNA sites, because the claims recite no more than a mere determination of their location on the isolated DNA sequence by means well known and conventional in the art.

Appellant points to claim 3 of Guidance Example 29 in support of their argument. Here too, Appellant's reliance on Example 29, does not show that the Board overlooked or misapprehended relevant points of fact or law in reaching the Decision.⁶ Claim 3 of the Example is deemed by the

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⁵ Page 3 of the Specification discloses, with respect to the term "modification," that the invention is directed to: "[A]nalyzing any one or more of the paternally- or maternally-derived DNA molecules or associated proteins for the presence or absence of modifications, wherein the step of analyzing determines whether any two modifications are present in *cis* on one chromosome, or in *trans* across two sister chromosomes."

⁶ The cited Example in the Guidance, although instructive, is not law that is binding on the Board's decisions. Nor did the cited Example exist at the time the Examiner's rejection on appeal, or when Appellant filed its

Guidance to be directed to patent-eligible subject matter because it is directed to a novel discovery beyond the phenomenon of nature to which the claim is otherwise directed. *See* Guidance 13 (Claim 3 is directed to a natural phenomenon). Specifically, the Guidance state that:

[Claim 3] requires detecting using a porcine anti-JUL-1 antibody. Prior to applicant's invention, and at the time the application was filed, the use of porcine antibodies in veterinary therapeutics was known to most scientists in the field. But significantly, there is no evidence that porcine antibodies were routinely or conventionally used to detect human proteins such as JUL-1. Thus, the claim's recitation of detecting JUL-1 using a porcine antibody is an unconventional step that is more than a mere instruction to "apply" the correlation and critical thinking step (the exception) using well-understood, routine or conventional techniques in the field. Whether taken alone or as a combination with the other additional elements, the recitation of detecting JUL-1 using a porcine anti-JUL-1 antibody yields a claim as a whole that amounts to significantly more than the exception itself.

Id. (emphasis added). As we have noted, Appellant's claims recite no such unconventional step for the determination of methylated sites on isolated DNA but, rather, broadly embrace any method, including, expressly, those well-known in the art.

To the extent Appellant invokes the Guidance in its Request, claim 2 of Example 29 is more apposite than claim 3 to our analysis. Exemplary claim 2 recites:

2. A method of diagnosing julitis in a patient, said method comprising:

relevant briefing on appeal. Appellant referred to the Example for the first time at oral hearing (*see* Hr'g Tr. 11 (dated Dec. 13, 2017)).

- a. obtaining a plasma sample from a human patient;
- b. detecting whether JUL-1 is present in the plasma sample by contacting the plasma sample with an anti-JUL-1 antibody and detecting binding between JUL-1 and the antibody; and
- c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected.

Guidance 10. We find exemplary claim 2 is more directly comparable to Appellant's claim 16 in that both contain: (1) an isolating/obtaining step; (2) an analysis step; and (3) a "determining/diagnosing" step.

The Guidance states that claim 2 is directed to patent-*ineligible* subject matter because:

Obtaining a sample in order to perform tests is well-understood, routine and conventional activity for those in the field of diagnostics. Further, the step is recited at a high level of generality such that it amounts to insignificant presolution activity, e.g., a mere data gathering step necessary to use the correlation. Detecting whether JUL-1 is present in the plasma sample merely instructs a scientist to use any detection technique with any generic anti-JUL-1 antibody. When recited at this high level of generality, there is no meaningful limitation, such as a particular or unconventional machine or a transformation of a particular article, in this step that distinguishes it from wellunderstood, routine, and conventional data gathering activity engaged in by scientists prior to applicant's invention, and at the time the application was filed, e.g., the routine and conventional techniques of detecting a protein using an antibody to that protein.

Guidance 12 (emphasis added). Similarly, and as we have noted *supra*, Appellant's claims are similarly directed to a "high level of generality,"

using "well-understood, routine, and *conventional data gathering activity*" (*id.* (emphasis added)) that is well-known in the art.

We are consequently not persuaded by Appellant's arguments that the Board failed to consider and address whether the combination of steps recited in the claims was novel in the art of DNA methylation and whether the limitations of the claim add "significantly more" than just the claimed natural phenomenon. For reasons explained, those matters were considered, yet we concluded that the claim elements alone and in combination failed to recite "significantly more" such that the added limitations "transform the nature of the claim" into a patent-eligible application. *Mayo*, 566 U.S. at 78.

D. The Board allegedly erred in finding that the mental step of making a determination of whether two methylated sites are *cis* or *trans* therefore constitutes an abstract idea

Appellant argues that the Board also erred in finding that: "[t]he mental step of making a determination of whether two methylated sites are cis or trans therefore constitutes an abstract idea, another judicially-created exception to Section 101...." Request 7 (quoting Decision 18). According to Appellant, the Board frames this alternatively as the claims requiring a "correlation step." *Id.* (citing Decision 17).

Appellant argues that the binary determination of whether two methylated sites are in a *cis* or *trans* relationship with one another is not accomplished by a mental step, but is rather performed by the step of "substantially isolating a DNA molecule from the biological sample, wherein the DNA molecule is an individual metaphase chromosome or a chromatid, or a fragment obtained therefrom" recited in claim 16. Request 7. According to Appellant, such isolation is not a mental step, but rather one

that requires significant activities in "the real world." *Id.* Appellant repeats the argument that it is the claimed isolation step that addresses the problem in the art that arose from the use of diploid genomic DNA for methylation analysis that was, at best, a statistical likelihood of the distribution of methyl groups along a single DNA strand. *Id.* In contrast, Appellant argues, as a result of the claimed invention, as a combination of steps that includes isolation of a maternal DNA strand from a paternal DNA strand, such ambiguity is resolved to a definitive assignment of the *cis* and *trans* relationships among methylation sites in diploid genome. *Id.* at 7–8.

We are not persuaded. The Board's conclusion that claim 16 contains an abstract "mental step" is not directed to the isolation of the DNA molecule, which is undeniably a non-abstract, practical procedure. Rather, the "mental step" of claim 16 is contained within the limitation reciting "determining whether any two methylated bases are present in cis on the DNA molecule." In the Decision, we expressly equated this step to the Federal Circuit's holding in *In re BRCA1 and BRCA2-Based Hereditary Cancer Test Patent Litigation*, 774 F.3d 755 (Fed. Cir. 2014):

In *BRCA*, the Federal Circuit held that method claims directed to the comparison of wild-type genetic sequences with a subject's genetic sequence were directed to the patent-ineligible abstract idea of comparing BRCA sequences and determining the existence of alterations. *BRCA*, 774 F.3d at 763. The Federal Circuit found, in this regard, that:

The methods, directed to identification of alterations of the gene, require merely comparing the patient's gene with the wild type and identifying any differences that arise. The number of covered comparisons is unlimited. The covered comparisons

are not restricted by the purpose of the comparison or the alteration being detected.

Id. (internal reference omitted).

Decision 17–18 (also citing *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 589–90 (2013)). Similarly, Appellant's claims require, in relevant part, only a mental determination whether "whether any two methylated bases are present in cis on the DNA molecule." We are therefore not persuaded the Board misapprehended or overlooked matters in concluding that claim 16's recitation of "determining whether any two methylated bases are present in cis on the DNA molecule" constitutes a mental step, and is therefore directed to an abstract idea.

To the extent Appellant raises the Guidance in support of the Request, here too, claim 2 of Example 29 is instructive. With respect to claim 2 of Example 29, the Guidance states that: "step c [(i.e., "diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected")] could be performed by a human using mental steps or basic critical thinking, which are types of activities that have been found by the courts to represent abstract ideas." Guidance 12. We similarly concluded that the final step of Appellant's independent claim 16 reciting: "determining whether any two methylated bases are present in cis on the DNA molecule" is likewise directed to a mental step or basic critical thinking and, therefore, to an abstract idea. As we expressly stated in the Decision:

In other words, claim 16 is directed to isolating and localizing, by any and all methods, methylated sites naturally occurring in cellular DNA and then making a mental assessment as to whether the localized methylated sites are *cis* or *trans*. This latter step require only a mental comparison step, *viz.*, a comparison of the attained results, to determine whether two methylated sites are either *cis* or

trans. As such, we conclude that this step is directed to a patent-ineligible abstract idea.

Decision 17. We are consequently not persuaded by Appellant's arguments in this respect.

E. The Board's alleged preemption analysis

Finally, Appellant argues that the Board's preemption analysis is already addressed by the two-step analysis developed under the case law and published by the USPTO. Request 8. Appellant points to the Federal Circuit's holding in *Ariosa* that: "The Supreme Court has made clear that the principle of preemption is the basis for the judicial exceptions to patentability." 788 F.3d at 1379. Appellant argues further that the Board should reconsider that, if its concern is that future, as yet undiscovered methods of DNA methylation analysis are foreclosed by claims 16, 20, and 22, claims 24–27 limit the claimed method to use of analytic methods including *the already extant technologies* recited in these claims at the time of filing of the present application, thus avoiding the preemption concerns set out by the Board. *Id.* (emphasis added).

We are not persuaded by this argument. Although the scope of preemption of Appellant's dependent claims may be narrower than the preemption created by Appellant's independent claims — preempting the natural phenomenon only when well-known assays are employed — that does not make the claims patent eligible. As explained above, merely appending conventional or routine steps (e.g., analyzing the DNA sequence via a routine assay), does not add significantly more to the natural phenomenon. Moreover, Appellant's contention simply reinforces that

claim 16 is much broader, and encompasses observation of the natural phenomenon through any means of "analyzing" the substantially isolated DNA molecule. Hence claim 16 risks preempting analysis of the natural phenomenon with "the already extant technologies," as well as with technologies that are presently unknown. We consequently are not persuaded by Appellant's arguments urging reversal of the Decision affirming the Examiner's rejection under 35 U.S.C. § 101.

CONCLUSION

We have considered the arguments raised by Appellant in the Request, but find none of these arguments persuasive that our original Decision was in error. We have addressed Appellant's arguments with respect to the claims on appeal, however, it is our view that Appellant has not identified any points that the Board has misapprehended or overlooked. We are still of the view that the Examiner did not err in reaching the legal conclusion of unpatentability under 35 U.S.C. § 101 based upon the record before us in the original appeal. We have therefore reconsidered our Decision, but decline to grant the relief requested. This Decision on Appellant's "Request for Rehearing" is deemed to incorporate our earlier Decision by reference. *See* 37 C.F.R. § 41.52(a)(1).

DECISION

We have granted Appellant's request to the extent that we have reconsidered our Decision, but we deny the requested relief with respect to making any changes therein. Appeal 2016-002684 Application 12/663,197

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv). *See also* 37 C.F.R. § 41.52(b).

DENIED